Renal denervation: latest trial shows technique is ineffective

Hypertension

I have written twice before in Irish Medical Times on the technique of renal sympathetic denervation that promised so much for patients with hypertension. First, in March 2012, while acknowledging that “percutaneous renal sympathetic denervation is undoubtedly a most promising cardiovascular intervention”, I cautioned that “we are far from being able to make any definitive conclusions”. Then in January this year, I highlighted the press release from Medtronic – the company that had sponsored three Symplicity trials – which warned that the technique had been shown to be ineffective in the biggest and best of these trials – the Symplicity HTN-3 trial. The results of the Symplicity HTN-1 and HTN-2 studies gave what were hailed by many as results so promising that the technique could be applied not only to patients with resistant hypertension, but also even to those with moderate blood pressure elevations. Renal denervation would not just cure hypertension, it would also improve cardiovascular outcome in other co-morbid conditions such as heart failure, diabetes mellitus, sleep apnoea, and arrhythmias. It was anticipated that studies would soon show that the procedure would allow patients to throw away their tablets and be permanently cured of hypertension.

But there were those who questioned the impetus for a treatment that was based on economic rather than scientific considerations. Meanwhile, the headlines rush to invest vast amounts of money in an unproven procedure continued. Guidelines were drawn up for the procedure and economic rather than scientific evidence was used to support the technique. The European regulatory bodies will have to question why they did not adopt the more cautious approach of the FDA in permitting use of the technique ahead of firm scientific evidence as to its benefit. More importantly perhaps, many patients – some 5,000 around the world, it is estimated – may now rightly ask if they might not have been spared from undergoing an ineffective procedure that was not without risk. In this regard, the Symplicity HTN-3 paper states that “there were no significant differences in safety between the two groups. More importantly, when data from ABPM were available they were seldom reported, and, when analyzed, did not show significant blood pressure reduction. Clinical scientists also warned that the procedure, although apparently safe in the short term, might induce changes in the future due to the more general effects of renal sympathetic denervation and possibly vascular damage to the renal arteries. Nonetheless, renal denervation moved on at an alarming pace with approval being granted in several European countries, but not in the US.

**Scientific facts**

Then on January 9, 2014, Medtronic issued a press release stating that its trial on renal denervation for treatment-resistant hypertension, Symplicity HTN-3, had failed to meet its primary efficacy end point, which was a reduction of 5mmHg in systolic blood pressure. This study, which had commenced in September 2011, randomised 355 treatment-resistant hypertension (office systolic blood pressure 160mmHg) to intervention with renal denervation and continuance of baseline anti-hypertensive medications, or a control group, where renal denervation would not be followed for five years after the procedure. The results of Symplicity HTN-3 confirmed this. The authors of the Symplicity HTN-3 study and the guidelines stipulated that the results of Symplicity HTN-3 should be followed for five years after the procedure. The results showed that the primary endpoint of systolic blood pressure reduction was not met

The major lesson to be learned from what could be called the renal denervation ‘debut’ is that the results of Symplicity HTN-3 were predictable and carefully conducted trials using ABPM rather than conventional blood pressure measurement could have saved millions of dollars in the medical device industry. The authors of the Symplicity HTN-3 study state that the results emphasise “the importance of conducting blinded trials with sham controls in the evaluation of new medical devices before their clinical adoption.”

The European regulatory bodies will have to question why they did not adopt the more cautious approach of the FDA in permitting use of the technique ahead of firm scientific evidence as to its benefit. More importantly perhaps, many patients – some 5,000 around the world, it is estimated – may now rightly ask if they might not have been spared from undergoing an ineffective procedure that was not without risk. In this regard, the Symplicity HTN-3 paper states that “there were no significant differences in safety between the two groups. More importantly perhaps, many patients – some 5,000 around the world, it is estimated – may now rightly ask if they might not have been spared from undergoing an ineffective procedure that was not without risk. In this regard, the Symplicity HTN-3 paper states that “there were no significant differences in safety between the two groups. More importantly perhaps, many patients – some 5,000 around the world, it is estimated – may now rightly ask if they might not have been spared from undergoing an ineffective procedure that was not without risk.

The Council on High Blood Pressure of the Irish Heart Foundation adopted the recommendation of the British Hypertension Society, the Irish Cardiovascular Intervention Society, the British Society for Interventional Radiology, the National Institute for Clinical Outcomes Research, the British Cardiovascular Society, and the Renal Association that there should be a temporary moratorium on renal denervation procedures for all patients with hypertension as part of routine care in Ireland until the data from Symplicity HTN-3 had been analysed. The full results of this study have just been published in the New England Journal of Medicine (www.nejm.org/NEJMoa1402670). They show, as anticipated, that the mean change in systolic blood pressure at six months was −14.2mmHg in the intervention group as compared with −11.2mmHg in the sham procedure group and the change in 24-hour ambulatory systolic blood pressure was −6.7mmHg in the intervention group compared with −4.7mmHg in the control group. All in all, statistically insignificant changes.

The conclusion was simply that “this blinded trial did not show a significant reduction of systolic blood pressure in patients with resistant hypertension six months after renal denervation as compared with a sham control. A ‘Dear physician’ letter was sent to Medtronic from this conclusion, and that while the primary endpoint result of the trial is not what we anticipated, we thank you for your ongoing support of the Medtronic Renal Denervation program.”

Presumably all bodies associated with providing guidance to practitioners, specialists and patients will now endorse the earlier recommen- dation of firm moratorium, and recommend that the procedure should no longer be performed in patients with hypertension.

**Lessons for the future**

The major lesson to be learned from what could be called the renal denervation ‘debut’ is that the results of Symplicity HTN-3 were predictable and carefully conducted trials using ABPM rather than conventional blood pressure measurement could have saved millions of dollars in the medical device industry. The authors of the Symplicity HTN-3 study state that the results emphasise “the importance of conducting blinded trials with sham controls in the evaluation of new medical devices before their clinical adoption.”

The European regulatory bodies will have to question why they did not adopt the more cautious approach of the FDA in permitting use of the technique ahead of firm scientific evidence as to its benefit. More importantly perhaps, many patients – some 5,000 around the world, it is estimated – may now rightly ask if they might not have been spared from undergoing an ineffective procedure that was not without risk. In this regard, the Symplicity HTN-3 paper states that “there were no significant differences in safety between the two groups. More importantly perhaps, many patients – some 5,000 around the world, it is estimated – may now rightly ask if they might not have been spared from undergoing an ineffective procedure that was not without risk.